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Long-term Prognosis for Individuals with Hypertension Undergoing Coronary Artery Calcium Scoring

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Abstract

Background—To examine the performance of coronary artery calcification (CAC) for stratifying long-term risk of death in asymptomatic hypertensive patients.

Methods and Results—8905 consecutive asymptomatic individuals without cardiovascular disease or diabetes who underwent CAC testing (mean age 53.3±10.5, 59.3% male) were followed for a mean of 14 years and categorized on the background of hypertension (in accordance with the 2014 Guidelines from the Joint National Committee 8) as well as age above or below 60 years. The prevalence and severity of CAC was higher for those with versus without hypertension ($P<0.001$), and the extent increased proportionally with advancing age ($P<0.001$). Following

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adjustment, the presence of CAC in patients above and below the age of 60 years was associated with worse prognosis for hypertensive (HR 7.74 [95% CI: 5.15-11.63] and HR 3.18 [95% CI: 2.42-4.19]) and normotensive (HR 4.83 [95% CI: 3.18-7.33] and HR 2.14 [95% CI: 1.61-2.85]), respectively. A zero CAC score was associated with a lower but persisting risk of mortality for hypertensives over the age of 60 years (HR 2.48 [95% CI: 1.50-4.08]); albeit, attenuating for those below the age of 60 years ($P=0.09$). In a “low risk” hypertensive population, a combined presence of hypertension and any CAC was associated with an almost five-fold (HR 4.68 [95% CI: 2.22-9.87]) risk of death.

Conclusion—Among asymptomatic hypertensive individuals, the presence and extent of CAC effectively identified individuals at heightened risk of mortality beyond conventional cardiovascular risk.

Keywords

Coronary artery calcium; hypertension; all-cause mortality; cardiac computed tomography

INTRODUCTION

One third of the adult population in the United States is affected by hypertension which remains a primary cause of mortality, accounting for approximately 14% of all US deaths.¹ Recently, the Joint National Committee set forth new guidelines regarding the clinical management of high blood pressure in adults.² These guidelines diverge from prior recommendations, with an age-stratified difference in recommendation for targeted blood pressure goals. Specifically, in hypertensive subjects younger than 60 years free from diabetes and kidney disease, these guidelines further state that the management of blood pressure should be determined based upon of clinical evaluation and use of the global cardiovascular risk assessment scores.

To this end, novel tools that effectively stratify risk of younger and older individuals with hypertension are needed.^{3,4} In short- and intermediate-term follow-up, the assessment of coronary artery calcification (CAC) scoring by computed tomography (CT) imaging is a non-invasive tool that enables accurate stratification of risk.⁵⁻⁹ Specifically, the presence,^{10,11} severity,¹² and progression^{13,14} of CAC has been shown to be independently associated with major adverse cardiovascular events¹⁰⁻¹⁵ and death,^{6,10,15-21} while a low risk of adverse outcomes has been observed in the absence of CAC.²²⁻²⁴ Nevertheless, these investigations lack insight towards the long-term efficacy of CAC for risk stratification, are limited in their focus among the hypertensive population, and have not yet examined the prognostic utility of CAC for hypertensive individuals when stratified by age.

To address this, in a large consecutive cohort of asymptomatic hypertensive individuals followed for 14 years, we sought to examine whether CAC could accurately stratify the risk of mortality

METHODS

Study population

The study cohort comprised 9715 consecutive asymptomatic individuals (41% female) without known coronary artery disease (CAD). All individuals referred by their physicians for electron beam computed tomography (EBCT) underwent CAC testing from a single site. Of 9715 individuals, 810 were excluded due to the presence of type 2 diabetes. The remaining 8905 individuals (mean age 53.3 ± 10.5 , 59.3% male) who represented the study population were divided into 2 groups based on hypertension status (Table 1). From the remaining cohort, we identified a sub-population of individuals without other traditional cardiovascular risk factors, as defined by the absence of dyslipidemia, family history of premature CAD, and smoking status ($n=781$). Those individuals are considered by definition,²² at low Framingham risk score (FRS) risk (herein referred to as low-risk subgroup). All screened individuals provided informed consent to undergo EBCT and the study received approval from the appropriate Human Investigations Committee.

Risk factor collection

All study participants were prospectively provided with a questionnaire for the collection of demographic characteristics as well as baseline cardiovascular risk factors. The following risk factors were considered in this study: 1) cigarette smoking was present if a subject was an active smoker at the time of scanning; 2) dyslipidemia was considered to be present for any individual reporting a history of high total cholesterol, high low density lipoprotein cholesterol, low high-density lipoprotein cholesterol, high triglycerides, or current use of lipid-lowering therapy; 3) diabetes was defined as baseline use of anti-diabetic medication or had a history of elevated blood glucose measurement of >126 mg/dl; 4) hypertension was defined as a self-reported history of high blood pressure or use of antihypertensive medication; and 5) family history of premature CAD was determined by asking individuals whether any member of their immediate family (parents or siblings) had a history of fatal or nonfatal myocardial infarction and/or coronary revascularization in a male relative <55 years or a female relative <65 years.

EBCT screening protocol

All subjects underwent EBCT on either a C-100 or C-150 Ultrafast CT scanner (GE-Imatron, South San Francisco, California). With a tomographic slice thickness of 3 mm, a total of approximately 40 sections were obtained beginning at the level of the carina and proceeding caudally to the level of the diaphragm. Images were obtained with a 100-ms/slice scanning time, with image acquisition electrocardiographically triggered at 60% to 80% of the R-R interval. A calcified lesion was defined as >3 contiguous pixels with a peak attenuation of at least 130 Hounsfield units. Each lesion was then scored using the method developed by Agatston et al.²⁵ (Agatston units).

Study outcome

The primary endpoint of this study was death from all-causes. Ascertainment of mortality status was conducted by individuals masked to baseline historical data and EBCT results,

and was verified using the Social Security Death Index. The Social Security Death Index is a national registry of all deaths that have occurred in the United States, allowing for 100% mortality ascertainment among study participants.

Statistical methods

Categorical variables are presented as counts with proportions (%) and continuous variables as mean \pm SD or median and interquartile range. The chi-square test was employed for comparison of categorical variables. Between-group comparisons for continuous variables were computed using the independent samples t-test or the Mann-Whitney U test as appropriate. A Kaplan-Meier survival curve with log-rank test was employed to compare survival rates for hypertensives versus normotensives above or below the age of 60 years, according to existing or absent CAC. Cox proportional hazard regression reporting hazard ratios (HR) with 95% confidence intervals (95% CI) were performed to examine the risk of death from all causes in the overall study population. Separately, we repeated the Cox analyses for the low-risk sub-group (i.e., with no traditional cardiovascular risk factors). All Cox models were stratified according to hypertension status, age above and below 60 years, and the presence or absence, as well as severity of CAC. Additionally, all Cox models adjusted for gender, smoking, dyslipidemia, and family history of premature CAD. We additionally tested the incremental prognostic value of CAC over and above an established risk algorithm, the Framingham Risk Score (FRS), using the area under the receiver operator characteristic curve (AUC). Further, we computed the net reclassification improvement (NRI),²⁶ which provides an estimate in percentage gain in reclassification for a pre-specified set of cut-off points. For the latter analysis, we chose risk categories based on low (<10%), intermediate (10% to 20%), and high (>20%) 10-year Framingham risk.²⁷ Statistical analyses were performed using SAS version 9.3 software (SAS Institute Inc., Cary, NC). A two-tailed P value <0.05 was considered statistically significant.

RESULTS

Study population

Demographic characteristics of the study cohort are summarized in Table 1. The mean follow-up was 14.6 \pm 1.0 years. There were 748 (8.4%) deaths in the study population; 408 (11.0%) occurred in hypertensive individuals with the remaining 340 (6.6%) deaths occurring in normotensive subjects. Overall, age, prevalent dyslipidemia, smoking status and family history of premature CAD, as well as CAC score ranged from 0- 8876 in 8905 patients. 4589 patients (51.5%) had a CAC score of zero and 4316 (48.5%) had non-zero CAC score, with a median score of 0 (interquartile range [IQR]: 0-60).

Distribution of CAC

Figure 1 describes the distribution of CAC severity according to individuals stratified by hypertension and age. The prevalence of zero CAC was greater among individuals without hypertension. Notably, the severity of CAC increased significantly on the background of hypertension and age (P<0.001).

CAC and all-cause mortality

Figure 2 reports the impact of CAC on mortality according to individuals stratified by hypertension and age. Incident mortality was lowest in normotensive individuals aged below 60 years without the presence of CAC, and highest for hypertensive individuals aged above 60 years. For individuals below the age of 60 years, there was no significant difference in the incidence of mortality for those with and without hypertension when the CAC was zero. Kaplan-Meier survival curves are reported in Figure 3. Irrespective of hypertension status and age, the presence of CAC was associated with worse prognosis (Figure A and B, both $P<0.001$). Of note, in hypertensive subjects, the absence of CAC was associated with a higher cumulative survival for individuals above 60 years old compared with individuals presenting with CAC (Figure 3 A). Moreover, among hypertensive subjects below 60 years old, cumulative survival was similar when compared with individuals without hypertension and CAC (Figure 3 B). In multivariable Cox analyses (Figure 4), the combined presence of CAC and hypertension was associated with the greatest risk of mortality, owing to an almost 8-fold (95% CI: 5.15-11.63) and greater than 3-fold (95% CI: 2.42-4.19) adjusted risk of mortality in individuals above and below the age of 60 years, respectively. In hypertensive individuals, the risk of death appeared to increase incrementally according to the severity of CAC – in older hypertensive subjects a CAC score above 100 was associated with the greatest risk of mortality owing to a more than 10-fold (HR 10.97; 95% CI 7.23-16.64) increase in the risk (Table 2). In contrast, in the absence of CAC, hypertension alone was associated with a lower, albeit significant heightened risk of mortality in those above the age of 60 years (HR 2.48; 95% CI 1.50-4.08); the association between hypertension and mortality was not significantly elevated among individuals below the age of 60 years (HR 1.35; 95% CI 0.95-1.91; $P=0.09$).

Utility of CAC for individuals without additional cardiovascular risk factors

We further investigated the utility of CAC for predicting the risk of mortality in a population of subjects without cardiac risk factors other than hypertension ($n=781$). CAC was present in 53% and 34% of individuals with and without hypertension, respectively. Cox proportional hazard regression analyses adjusting for age and gender indicated the presence of hypertension alone was not associated with an increased risk of mortality when CAC was absent (Figure 4). However, the combined presence of hypertension and CAC conferred an almost 5-fold adjusted risk of death in these apparently “low-risk” individuals. Albeit, this observed increased risk in mortality appeared to be independent on CAC severity (Table 3).

Discrimination and reclassification

Compared with the FRS alone, discrimination improved significantly (AUC [Area under the receiver operating characteristics curve] 0.71 versus 0.62; $p < 0.001$) when CAC was added to the FRS (Figure 5). The addition of CAC to the FRS further resulted in a 37% and 13% correct reclassification of individuals to a different risk category that defined the experience or no experience of an event, respectively ($P<0.001$). The net NRI was actually 23.3%.

DISCUSSION

In the present study, we found CAC to be an efficacious tool for long-term identification and exclusion of individuals with hypertension who are at heightened risk of mortality. Our study highlights three main findings. First, in hypertensive individuals aged above 60 years, death from all-causes dramatically increased in proportion to the severity of CAC. Second, among younger adults (i.e., below the age of 60 years), the effect of the presence of CAC was considerably less pronounced – importantly the absence of CAC was associated with an excellent long-term survival even in presence of hypertension, beyond other conventional risk factors. Third, in a selected “low risk” population the presence of CAC considerably increased the risk of death while correctly reclassifying individuals from low-to-intermediate into a higher risk category.

These findings emphasize the use of a risk marker such as CAC as additive to conventional risk factors for identifying patient-specific risk of future adverse cardiovascular events. While the utility of CAC in the management of hypertensive individuals was not accounted for by the JNC 8 guidelines, based on the current study findings, CAC evaluation may assist in driving the diagnostic and therapeutic management of this category of individuals. CAC has the potential to identify a heightened at-risk group of hypertensive individuals greater than 60 years who may require blood pressure lowering even further below the current guidelines of 150/90 mmHg. Moreover, even among asymptomatic hypertensive individuals with no additional traditional cardiovascular risk factors, the presence and severity of CAC was effective in identifying increased risk of death. This ostensibly “low risk” population may easily be overlooked by traditional risk factor scoring, and yet the prevalence of CAC was common in this cohort. On the other hand, in hypertensive subjects below the age of 60 years, the absence of CAC demonstrated excellent long-term prognosis suggesting those individuals might benefit from milder treatment, with higher therapeutic targets supplemented by lifestyle modifications and fewer clinical re-evaluations.

Whether CAC can be used to further guide patient-specific therapies beyond conventional cardiovascular risk alone is beyond the scope of this study, but nevertheless, evokes the possibility that a CAC-guided approach to treatment may improve future clinical outcomes. Studies examining this hypothesis now appear warranted.

Importantly, the present study findings are directly additive to the current body of evidence that has examined the use of CAC in the asymptomatic hypertension population^{20,28}. First, we followed all individuals with hypertension—irrespective of their level of risk—for nearly 15 years. Prior studies have focused primarily upon intermediate-risk patients, with very few event analyses performed for low-risk individuals (e.g., 1 or 2 clinical events).^{29,30} In contrast, given our study sample size and duration of follow-up, we observed a substantially elevated risk of mortality even amongst individuals considered low-risk by the FRS but with present CAC. Finally, the inclusion of CAC demonstrated significantly improved risk stratification and discrimination above and beyond the FRS, underlining the high prognostic utility of this clinical parameter in an asymptomatic hypertension population.

This study is not without limitations. First, we employed all-cause mortality as a primary endpoint in this study, given its freedom from ascertainment and knowledge bias. However, it remains likely that coronary-specific deaths that occurred for individuals within this study were diluted from deaths from other causes.³¹ Importantly, however, this relative dilution likely contributed to an under-, rather than over-estimation, of the effect of the current study findings. Second, the effects of CAC scoring on incident changes to medical therapy and/or lifestyle modification are not known in this study, and their mitigating effects to reduce (or increase) mortality rates is unknown. Third, the self-reporting of risk factors, in particular diabetes, beyond current established guidelines should be considered another limitation of this investigation - though prior studies have demonstrated the reliability of self-reporting cardiovascular risk factors.³² Finally, despite the large study sample, long-term follow-up and prospective evaluation of study individuals, the single-center nature of the present study may nevertheless be associated with a reduced generalizability in lieu of multicenter studies. On the whole, individuals were enrolled based on a referral for EBCT – therefore, the current study individuals could be deemed to be somewhat at higher risk, which could have influenced the general applicability of our findings to other apparently healthy populations.

In conclusion, in a long-term follow-up of nearly 15 years, the presence and severity of CAC effectively prognosticates future mortality for asymptomatic hypertensive individuals, which were more pronounced in subjects greater than 60 years. On the other hand, the absence of CAC in hypertensive individuals aged below 60 years confers a 15-year survival similar to non-hypertensive subjects. This study advocates the possibility that a CAC-driven approach to treatment may improve clinical outcomes in the future. Prospective studies examining this hypothesis now appear necessary.

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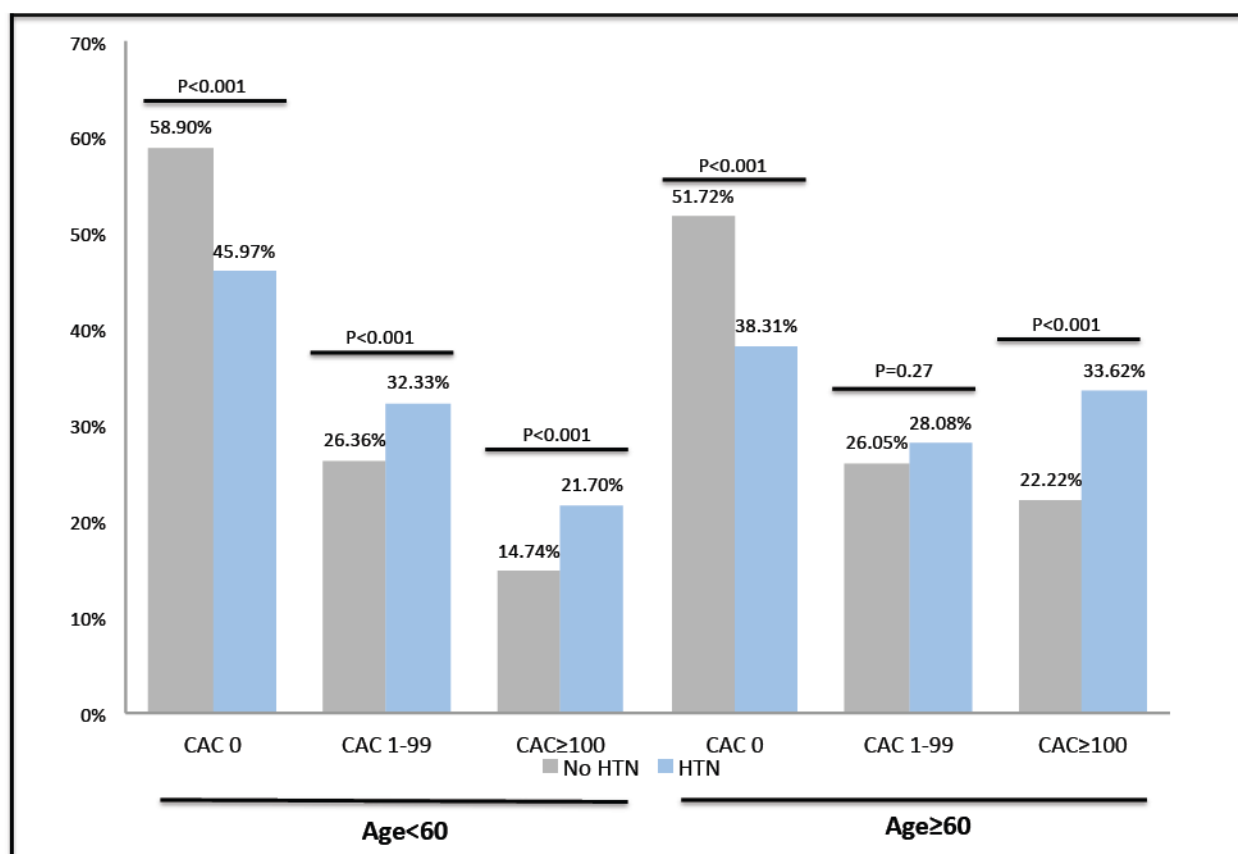


Figure 1.
Severity of coronary artery calcification among hypertensive and non-hypertensive individuals stratified by age above and below 60 years.

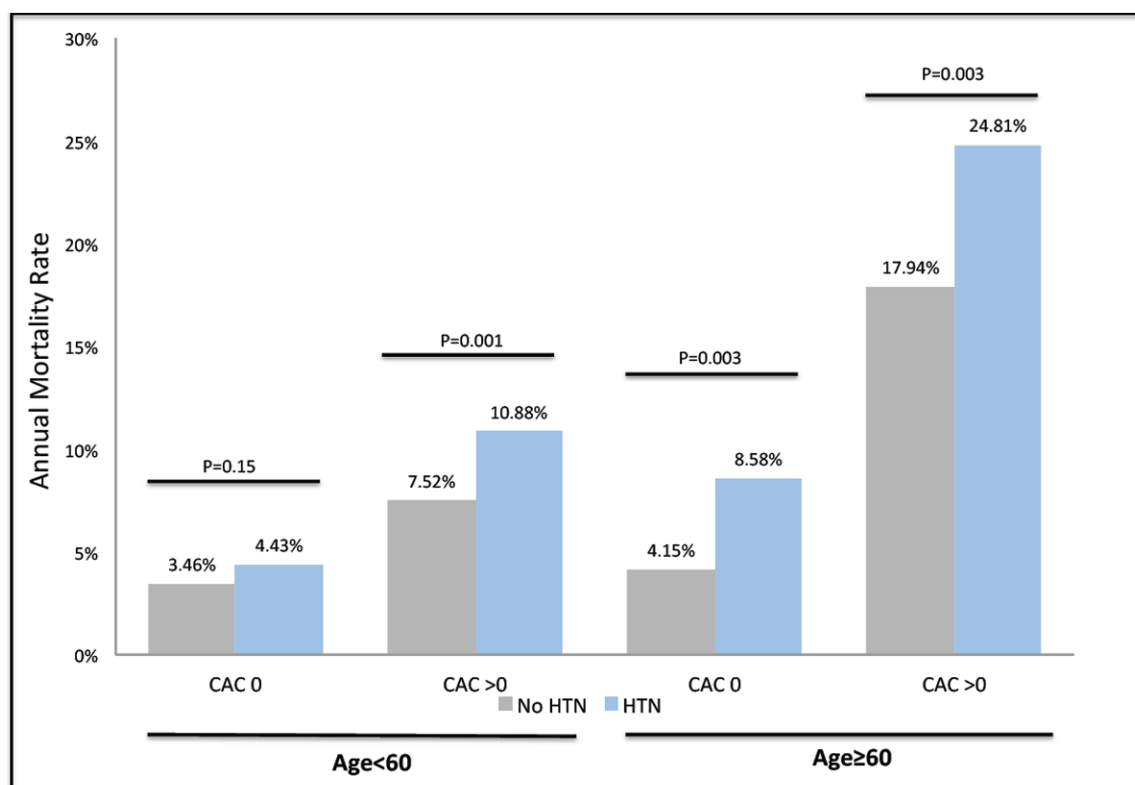


Figure 2.
Annual mortality rate according to hypertension and coronary artery calcification in individuals above and below the age of 60 years

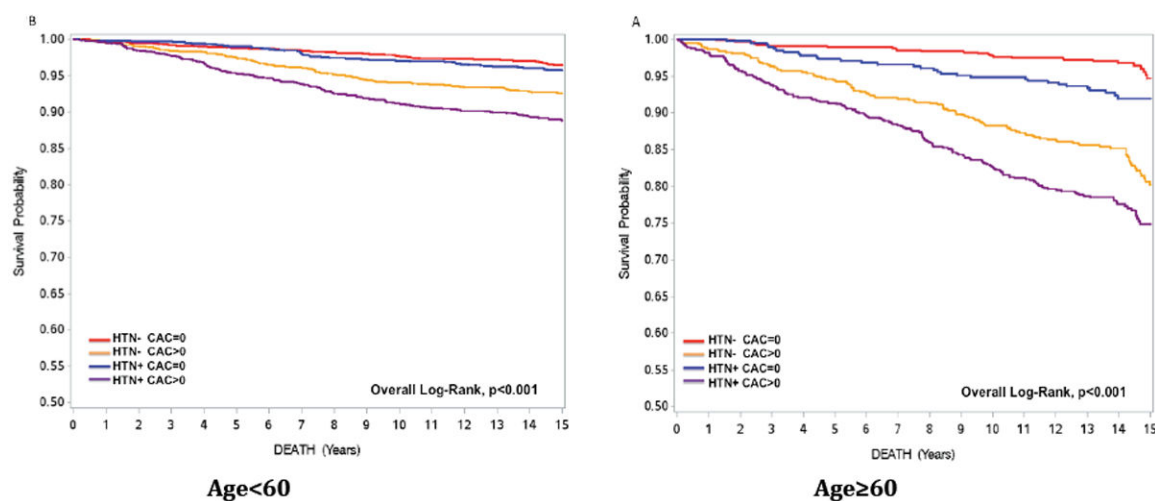


Figure 3. Kaplan-Meier survival curves for all-cause mortality according to categories of hypertension and coronary artery calcification in individuals above (a) and below (b) the age of 60 years

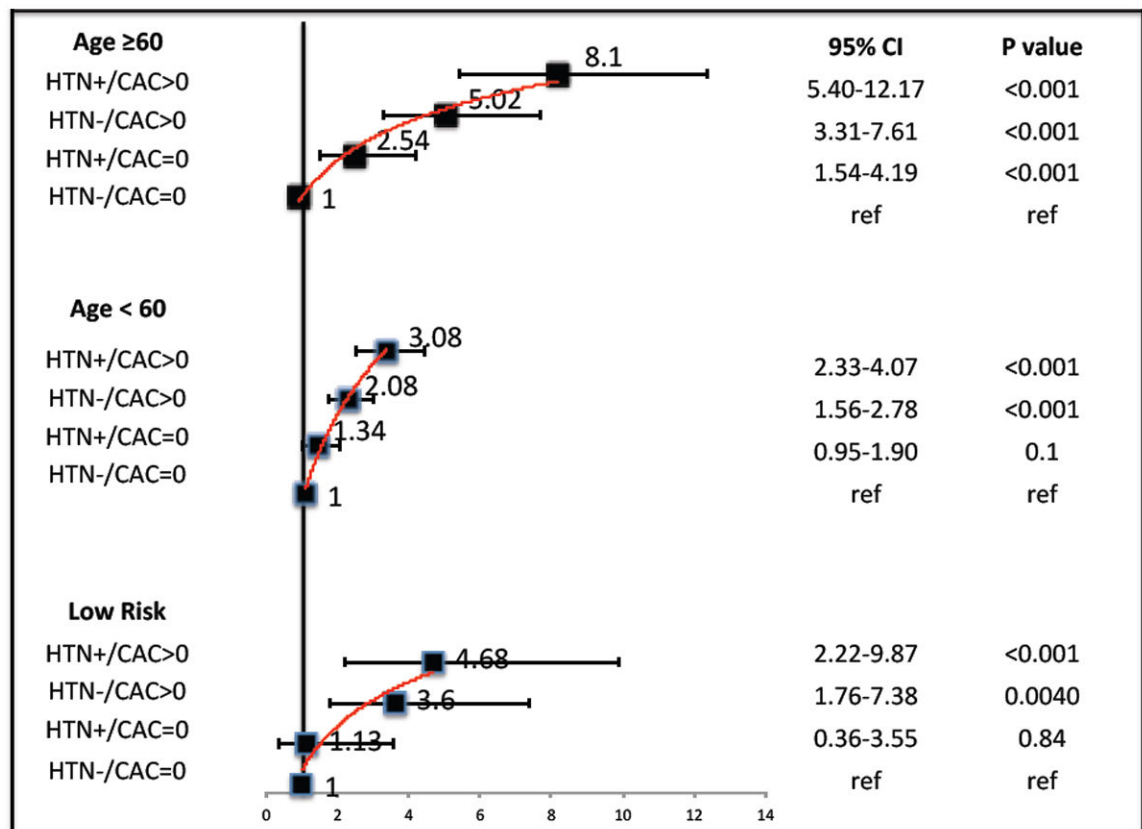


Figure 4.

Risk of all-cause mortality among individuals stratified by hypertension and coronary artery calcification for those above and below the age of 60 years, as well as without additional cardiac risk factors (low-risk category). Hazard ratios with 95% confidence intervals are reported. Models adjusted for gender, smoking, dyslipidemia, and family history of premature coronary artery disease. Low-risk category was adjusted for just age and gender.

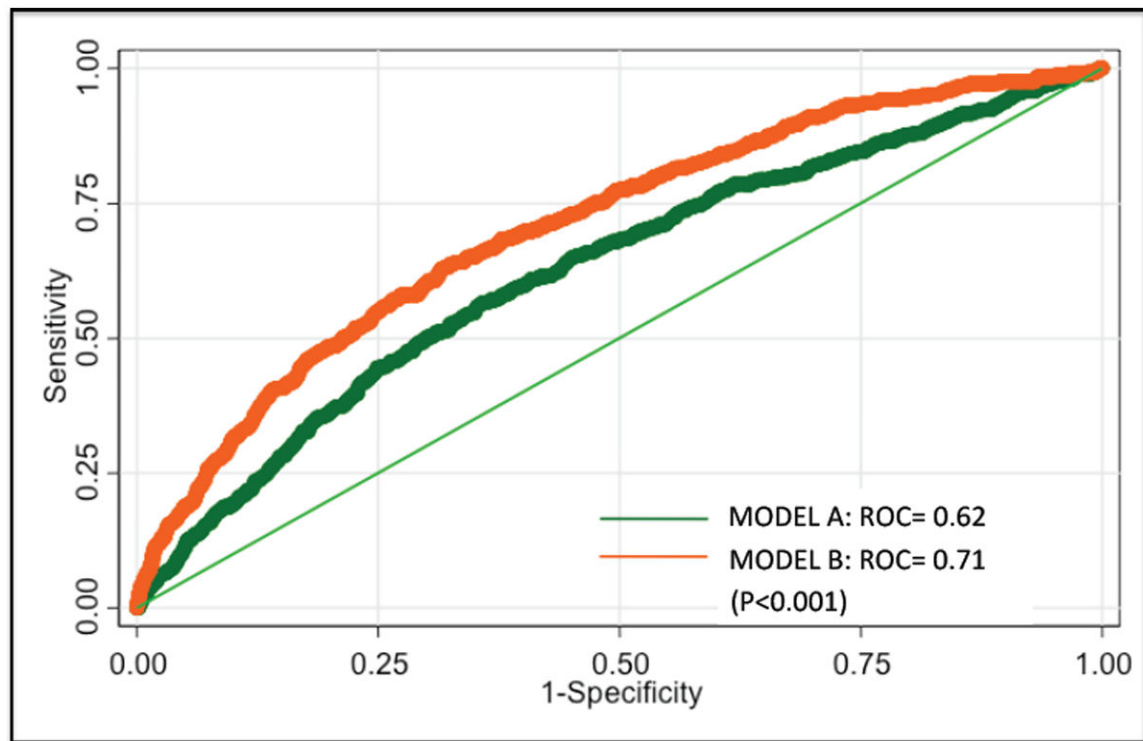


Figure 5.

Discrimination for all-cause mortality according to the area under the receiver operating characteristic curve (ROC) using the coronary artery calcium score. Model A represents the Framingham Risk Score (base model). Model B included the base model as well as log coronary artery calcium score.

Table 1

Clinical characteristics of the study population

Variable	Total n (N=8905)	Hypertension status				Classified by age			
		All subjects		<60 years		60 years		P value	
		No (N=5186)	Yes (N=3719)	No (N=3881)	Yes (N=2654)	No (N=1305)	Yes (N=1065)	P value	
Mean follow-up (years)	14.6±1.0	14.6±1.0	14.6±1.0	14.6±1.0	14.6±1.1	14.5±1.1	14.5±1.1	0.32	0.55
Death events (%)	748 (8.4)	340 (6.6)	408 (11.0)	199 (5.1)	210 (7.9)	141 (10.8)	198 (18.6)	<0.001	<0.001
Age (years)	53.3±10.5	52.8±10.5	53.9±10.3	48.1±6.9	48.8±6.7	66.9±5.8	66.6±5.4	<0.001	0.34
Gender (female)	3621 (40.7)	2123 (40.9)	1498 (10.3)	1478 (38.1)	935 (35.2)	645 (49.4)	563 (52.9)	0.0189	0.0958
Dyslipidemia	5540 (62.2)	2975 (57.4)	2565 (69.0)	2227 (57.4)	1823 (68.7)	748 (57.3)	742 (69.7)	<0.001	<0.001
Current smokers	3473 (39.0)	1965 (37.9)	1508 (40.6)	1474 (38.0)	1081 (40.7)	491 (37.6)	427 (40.1)	0.0252	0.2196
Family history premature CAD	6140 (69.0)	3491 (67.3)	2649 (71.2)	2658 (68.5)	1879 (70.8)	833 (63.8)	770 (72.3)	0.0464	<0.001
CAC > 0 (%)	4316 (48.5)	2225 (42.9)	2091 (56.2)	1595 (41.1)	1434 (54.0)	630 (48.3)	657 (61.7)	<0.001	<0.001

CAD: Coronary artery disease; CAC: Coronary artery calcification.

Table 2

15-year survival stratified by hypertension status and coronary artery calcium score in individuals above and below 60 years.

	Unadjusted HR		Adjusted HR*	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value
Age ≥ 60				
No Hypertension				
CAC 0	1.00 (ref)		1.00 (ref)	
CAC 1-99	3.36 (2.10-5.39)	<0.001	3.47 (2.16-5.57)	<0.001
CAC ≥100	6.34 (4.08-9.87)	<0.001	6.58 (4.22-10.25)	<0.001
Hypertension				
CAC 0	2.15 (1.31-3.53)	0.003	2.45 (1.49-4.05)	<0.001
CAC 1-99	3.62 (2.24-5.85)	<0.001	4.17 (2.57-6.77)	<0.001
CAC ≥100	10.21 (6.75-15.43)	<0.001	10.97 (7.23-16.64)	<0.001
Age<60				
No Hypertension				
CAC 0	1.00 (ref)		1.00 (ref)	
CAC 1-99	1.87 (1.34-2.60)	<0.001	1.79 (1.28-2.49)	0.001
CAC ≥100	3.05 (2.16-4.30)	<0.001	2.80 (1.98-3.96)	<0.001
Hypertension				
CAC 0	1.29 (0.91-1.82)	0.15	1.35 (0.95-1.91)	0.09
CAC 1-99	2.79 (2.04-3.82)	<0.001	2.75 (2.00-3.77)	<0.001
CAC ≥100	4.24 (3.10-5.81)	<0.001	3.85 (2.79-5.30)	<0.001

* Adjusted for gender, smoking, dyslipidemia, and family history of premature coronary artery disease.

HR hazard ratio; 95% confidence interval; CAC Coronary artery calcium score.

Table 3

15-year survival stratified by hypertension status and coronary artery calcium in the “low risk” population

	Unadjusted HR		Adjusted HR[*]	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value
No Hypertension				
CAC 0	1.00 (ref)		1.00 (ref)	
CAC 1-99	2.04 (0.82-5.07)	0.13	1.80 (0.72-4.50)	0.21
CAC 100	10.63 (4.98-22.71)	<0.001	6.97 (3.22-15.09)	<0.001
Hypertension				
CAC 0	1.17 (0.37-3.67)	0.79	1.13 (0.36-3.55)	0.84
CAC 1-99	5.16 (2.24-11.91)	<0.001	5.00 (2.16-11.54)	<0.001
CAC 100	5.93 (2.39-14.76)	<0.001	4.34 (1.73-10.89)	0.002

* Adjusted for age and gender.

HR hazard ratio

CAC Coronary artery calcium score